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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,206	06/21/2001	Sunao Hisada	400683	8134

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EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/622,206	HISADA ET AL.	
	Examiner	Art Unit	
	James L. Grun	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2005 and 24 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,8 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,8 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 24 June 2005 and, as directed therein, the amendment filed 28 March 2005 have been entered.

Claim 22 is newly added. Claims 2, 6, 7, and 9-21 have been cancelled. Claims 1, 3-5, 8, and 22 remain in the case.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-5, 8, and 22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 3-5, 8, and 22, "the amount of antigen" lacks antecedent basis. It is not clear what is encompassed by "antibody...being modified" because it is not clear what the original structure for comparison encompasses.

In claim 8, it is not clear what sequences or characteristics applicant intends as encompassed by a "gene." There is no accepted definition of the term in the art or provided in the specification such that one would readily know or be able to predict or envision what structure is encompassed within the metes and bounds of the invention as claimed. A gene

sequence as found in the genome may include introns and specific splice donor/acceptor sequences which are not disclosed by the description merely of an encoding sequence.

Applicant's arguments filed 28 March 2005 and 24 June 2005 have been fully considered but they are not deemed to be persuasive. Notwithstanding applicant's assertions to the contrary, rejections under this statute have not been obviated by applicant's amendments for the reasons set forth above.

Claims 1, 3-5, 8, and 22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Karger et al. (U.S. Pat. No. 5,348,633) in view of Fuchs et al. (U.S. Pat. No. 5,630,924) and Chen et al. (Electrophoresis 15: 13, 1994) for reasons similar to those of record in the prior rejection of the similar subject matter of claims 1-5 and 8.

Karger et al. teach a method for quantitative detection of trace amounts of analyte wherein an antibody Fab' fragment specific for analyte is fluorescently labeled at a single reactive sulfhydryl group in a chemically-modified CH1/hinge region of the fragment, the fragment is reacted with sample to form an immune complex with any analyte present, the complex is concentrated and separated from unreacted components using capillary electrophoretic methods such as isoelectric focusing, and the concentrated and separated complex is quantitatively detected as an indication of level of analyte by detecting the level of the fluorescent signal of the immune complex. The reference implicitly teaches Fab' antibodies having uniform isoelectric points because isoelectric focusing is used to purify the antibody fragments for use (see e.g. col. 6). This is shown by applicant in Figure 8 of the instant application as is set forth in the Japanese patent application of Karger et al. related to Pat. No.

5,348,633. In contrast to the invention as instantly claimed, the patent of Karger et al. does not disclose charge-modified antibodies.

Fuchs et al. teach that it was well known in the art that the electrophoretic mobility of a labeled antibody in capillary electrophoretic methods could be tailored by attaching charged groups to the labeled antibody (see e.g. col. 2), teach methods of labeling and charge modification of monoclonal antibody fragments, for example by the addition of charged amino acid sequences (see e.g. cols. 11-12), and teach that fragments could be purified before use by a method such as isoelectric focusing (see e.g. cols. 23-26).

Chen et al. teach that it is possible to achieve effective separation of antigen or antibody from antigen-antibody complexes by modulating the electrophoretic mobility of the antigen or antibody with modification with charge-bearing organic molecules (see e.g. pages 14 and 19). The reference teaches that use of excess modified labeled monoclonal antibody in the capillary electrophoresis methods of the reference would require only a single antibody and obviate the need for a second sandwiching antibody (see e.g. page 21). Chen et al. is also cited in Fuchs et al.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have provided a charge-modified labeled monoclonal antibody fragment of uniform isoelectric point in the methods of Karger et al. because Fuchs et al. teach that charge modification of labeled antibody fragments was well known in the capillary electrophoresis art for a variety of electrophoretic mobility tailoring purposes, such as to achieve effective separations of bound and free reagents with the use of a single charge-modified labeled monoclonal antibody as taught in Chen et al., and both Karger et al. and Fuchs et al. teach that

purification of such antibody fragments can involve isoelectric focusing which one of ordinary skill in the art would have reasonably expected to have provided a uniform isoelectric point to the purified antibody fragment purified thereby. One would have expected the method, as modified, to function in view of the exemplification of functional methods in Karger et al. or Chen et al. The process of providing a given reagent does not serve to differentiate an identical reagent provided by another method and there is nothing on the record which provides evidence of a difference between the antibody fragments of the prior art provided by chemical modifications and those as instantly claimed provided recombinantly.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 8 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karger et al. in view of Fuchs et al. and Chen et al. as applied to claims 1, 3-5, 8, and 22 above, and further in view of Shimura et al. (Anal. Chem. 66: 9, 1994), Bodmer et al. (WO 89/01974), and Cabilly et al. (U.S. Pat. No. 4,816,567) for reasons similar to those of record in the prior rejection of the similar subject matter of claims 2 and 8.

The teachings of Karger et al., Fuchs et al., and Chen et al. are as set forth above and differ from the invention as instantly claimed in not teaching providing modified antibody fragments by recombinant methods.

Shimura et al. teach the method of Karger et al. for a particular application and teach that the availability of genetically engineered Fab or Fv fragments would provide advantages for the

purity and facility of labeling of the fluorescent immune probes for the method (see e.g. page 15).

Bodmer et al teach recombinant methods for making antibody molecules altered in the hinge region associated with the CH1 region of the molecule, in particular for reducing the number of cysteine residues to one for reporter molecule attachment (see e.g. page 7). The methods may also substitute alternative sequences for those naturally present in a given antibody molecule hinge region. The reference teaches that methods of grafting complementarity-determining regions onto other framework regions to produce chimeric antibodies were known to the art.

Cabilly et al. teach recombinant methods for the production of chimeric antibodies or antibody fragments for the benefits taught therein

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have produced the modified antibody fragments of Karger et al. in view of Fuchs et al. and Chen et al. recombinantly because Shimura et al. provides the direct suggestion to do so, Bodmer et al. teach the recombinant formation of antibody molecules with altered hinge regions having, in particular, a single reactive cysteine residue as desired for labeling by Karger et al. and Cabilly et al. teach the benefits of recombinant production of altered antibody molecules and fragments. One would have had obvious motivation to have produced cloned molecules for the benefits of providing a potentially unlimited source of homogeneous reagent for use, to obviate the need for periodic chemical modification of new batches of reagent for use, and for purity and facility of labeling as taught in Shimura et al.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Applicant's arguments filed 28 March 2005 and 24 June 2005 have been fully considered but they are not deemed to be persuasive.

Applicant urges that Karger et al., as modified, teach a complicated method of forming the labeled antibody fragments. This is not found persuasive for the reasons of record that the process of providing a given reagent does not serve to differentiate an identical reagent provided by another method and there is nothing on the record which provides evidence of a difference between the antibody fragments of the prior art provided by chemical modifications and those as instantly claimed provided recombinantly. Moreover the combination of Karger et al. in view of Fuchs et al. and Chen et al., and further in view of Shimura et al., Bodmer et al., and Cabilly et al. teaches, for the reasons of record, recombinant production of the antibody fragments.

Applicant urges that Fuchs et al. teach away from the instant invention. This is not found persuasive for a number of reasons. Firstly, applicant's argument is not found persuasive because Fuchs et al. teach charge modification of a single labeled antibody for exactly the reasons suggested in the instant invention, different mobility of charged and uncharged antibody. In this regard, as argued unpersuasively by applicant in a previous response (because limitations from the specification are not read into the claims), an unclaimed limitation of the method of the invention allows separations of antigen, charge-modified labeled antibody fragment, and labeled antibody-antigen complex when the isoelectric points of the unmodified labeled antibody fragment and the antigen are the same or close to the same because of different mobility of

charged and uncharged antibody. The argument is also not found persuasive because applicant's arguments are drawn to additional disclosure of the reference not relied upon in the reasons for rejection. The passages in Fuchs et al. relied upon by the examiner teach generic antibody charge or labeling modification methods and teach that charge modification of a labeled antibody in capillary electrophoretic methods was known to the art for single antibody methods (e.g. Chen et al.). As set forth, Chen et al., as also cited in Fuchs et al., is relied upon to teach the desirability of charge modification of the labeled antibody in the method for achieving effective bound and free separation. Single antibody methods, as taught in Karger et al., Shimura et al., and Chen et al., have additional advantages, not related to the separation of labeled and unlabeled antibody argued in the reference and by applicant, over the sandwich method taught in Fuchs et al., which was and is not relied upon by the examiner in the grounds of rejection. As set forth, one would have expected a functional assay because the methods of Karger et al. or Shimura et al. or Chen et al., as modified, which rely upon differences in mobility of the labeled antibody and the labeled antibody-antigen complex, were fully functional for separations.

Applicant urges that the references do not specifically teach linking the charge-modifying moiety to the C terminus of the light chain. This is not found persuasive because it is not clear what the original structure for comparison encompasses. One would have expected many changes in charge to both heavy and/or light chains by the modifications taught in the references such as in chimeric antibodies, or in CDR grafted antibodies, or in the substitution of alternative sequences for those naturally present in a given antibody molecule CH1/hinge region, or in chemical modification of the CH1/hinge region, or in a single chain Fv fragment, or in antibody maturation in a host prior to fusion to generate a particular monoclonal antibody. Applicant

further urges that the modifications taught in the references would not yield fragments of uniform isoelectric point. This is not found persuasive for the reasons of record that both Karger et al. and Fuchs et al. teach that purification of such antibody fragments can involve isoelectric focusing which one of ordinary skill in the art would have reasonably expected to have provided a uniform isoelectric point to the purified antibody fragment purified thereby.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JLG

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August 29, 2005

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